REMARKS

Claims 69-75, 82-93, 95, and 100-119 are now pending in the application, claims 94 and 96-99 having been canceled by the present amendment and new claims 100-119 having been added. Claims 69, 83, 84, 91, and 95 have been amended.

Support for the amendment can be found throughout the specification. Amended **claim 69** and new **claim 100** are supported by the specification at, for example, page 3, lines 3-8; page 7, lines 2-6; page 9, lines 6-9; and page 20, lines 18-20. Support for amended **claim 83** and new **claim 108** can be found at, for example, page 10, lines 15-19; page 20, lines 18-20; and page 36, lines 6-14. Support for amended **claim 84** and new **claim 109** can be found at, for example, page 7, lines 2-6; page 9, lines 6-9; and page 35, lines 25-32. Support for amended **claim 91** and new **claim 116** can be found, for example, at page 35, lines 27-32. Support for amended **claim 95** and new **claim 119** can be found, for example, at page 3, lines 3-8.

New **claims 100-119** were added in response to the Examiner's request to separate claims that define the NES1 gene with respect to the nucleotide sequence of SEQ ID NO:2 from claims that define the gene with respect to the polypeptide it encodes (SEQ ID NO:1). The limitations of new claims 101-108 are similar to those of pending claims 70-75, 82, and 83, respectively. The limitations of new claims 110-119 are similar to pending claims 85-93 and 95, respectively.

No new matter has been added.

Any subject matter that is canceled is canceled without prejudice to Applicant's right to pursue the subject matter of the claims in a continuation application.

Applicant wishes to extend her appreciation to Examiner Nashed for his time and consideration during the telephone interview of December 20, 2004, with Applicant's representatives, Lee Crews and Allyson Hatton. The Examiner appeared to be inclined to allow claims limited to a NES1 gene comprising a coding sequence that encodes a polypeptide that is (a) at least 95% identical to SEQ ID NO:1 or (b) at least 95% identical to SEQ ID NO:2 so long as that subject matter is free of the prior art.

Because the present amendment is believed to place the claims in condition for allowance, or, at least, to reduce the issues for appeal, Applicant respectfully requests that it be entered, even though a final Office Action has been received.

Restriction Requirement

The Examiner has found that "the subject matter of claims 96-99 is new in this application, and is subjected to restriction requirement from the pending methods claims" (Office action at page 2). In response, Applicant has canceled claims 96-99.

Obviousness-type Double Patenting

The Examiner has rejected claims 69-75 and 82-95 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 10-14 of U.S. Patent No. 6,153,387 (Office action at page 2).

Should the Examiner remain persuaded that the claims of the present application are not patentably distinct (from those of U.S. Patent No. 6,153,387) when otherwise in condition for allowance, Applicant will file a terminal disclaimer.

35 U.S.C. § 112, Paragraph 1

Written Description: The Examiner rejected claims 69-75, 82-93, and 95 as (Office action at page 3):

> containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention ...

The Examiner maintained the rejection "for the reasons set forth in the prior Office action" (Office action at page 3). In that action, the Examiner stated that the specification "only provides a single representative species from human cell lines, e.g., the NES1 gene of SEQ ID NO:2" and that, given the "lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention" (Office action dated December 19, 2003, at page 4).

In the instant Office action, the Examiner states, "[t]he claims are not limited to the human NES1 gene of which SEQ ID NO:2 is a cDNA product" and then reproduces a passage from Applicant's specification concerning NES1 polypeptides. That passage is reproduced here for easy reference (and appears in the specification at pages 6-7):

> By "NES1 polypeptide" is meant an amino acid sequence, which is a cell cycle-regulated serine protease whose expression negatively correlates with the presence of malignant epithelial cells. Preferably, such a polypeptide has an amino acid sequence, which is at least 45%, preferably 60%, and most preferably 85% or even 95% identical to the amino acid sequence of the NES1 protein of Fig. 10 (SEQ ID NO:1).

According to the Examiner, SEQ ID NO:2 is the only species within the genus of NES1 polypeptides that is adequately described (Office action at page 3). The Examiner then concludes (Office action at pages 3-4):

> While the methods claimed are limited to human NES1 gene and the biological sample is from human, one of ordinary skill in the art would still recognize that applicant has not fully described the entire genus of the NES1 genes. To overcome the above rejection, the claim must contain a structural feature of the NES1 gene accompanied by a functional feature.

In view of the present amendment and the remarks that follow, the Examiner is respectfully asked to reconsider and withdraw this ground for rejection. Applicant's remarks include reference to the Written Description Guidelines (Federal Register, vol. 66, no. 4, Notices pp. 1099-1111, January 5, 2001), even though they do not carry the force of law. In addition, Applicant provides relevant court decisions regarding the statutory requirement for an adequate written description, and it is in accordance with those decisions that the present ground for rejection should be withdrawn.

An Applicant's specification should clearly convey that he or she invented the claimed subject matter. *In re Barker*, 559 F.2d 588 (CCPA 1977). The specification must put the public in possession of that subject matter. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997), *cert. denied* 523 U.S. 1089 (1998). It is that – the conveyance of the invention to the

public – that is given in exchange for the right to exclude others from practicing the invention for the duration of the patent's term. *Eldred v. Ashcroft*, 537 U.S. 186 (2003).

An adequate description is one that describes the claimed invention in sufficient detail that one of ordinary skill in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). Possession may be shown in a variety of ways. For example, possession can be found where an Applicant presents drawings of the claimed invention (as in *Vas-Cath*) or structural chemical formulas. An Applicant may also describe distinguishing identifying characteristics. *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55 (1998); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200 (Fed. Cir. 1991) (one may define a compound by "whatever characteristics sufficiently distinguish it").

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by: actual reduction to practice; reduction to drawings; or disclosure of relevant identifying characteristics. MPEP at 2163(3)(a)(ii), citing *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997). A "representative number of species" means that the species that are adequately described are representative of the entire genus. MPEP at 2163(3)(a)(ii), citing *Enzo Biochem,* 323 F.3d at 966, 63 USPQ2d at 1615 and *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004).

The Examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. MPEP at 2163(II)(A), citing *Wertheim*, 541 F.2d 257 (CCPA 1976).

As noted above, in the present case, the Examiner has argued that Applicant has failed to provide a representative number of NES1 sequences. The Examiner states, "[f]rom the above genus of nucleic acid encoding NES1 polypeptide" – *i.e.*, the genus described in the excerpt from pages 6-7 of the specification – "only the species of SEQ ID NO:2 is described" (Office action at page 3).

This comparison (between the referenced passage in the specification (as the genus) and SEQ ID NO:2 (as the species)) is not appropriate. A rejection under the first paragraph of § 112 is valid

only where an Applicant has not adequately described the invention *that is claimed* (as is true for rejections based on enablement, novelty, and obviousness; what must be enabled, novel, and non-obvious is the subject matter claimed). Thus, here, the question is whether Applicant has adequately described how to carry out the diagnostic methods of the invention within the limits set out in the present claims.

Those claims cover methods of "determining whether a human has a carcinoma or an increased likelihood of developing a carcinoma" by examining the expression or sequence of a human NES1 gene that exhibits a certain degree of identity to a reference sequence. More specifically, the method claimed requires examination of a NES1 gene, within a biological sample obtained from a human patient, that includes a coding sequence that either (a) encodes a polypeptide that is at least 95% identical to SEQ ID NO:1 (*see* claims 69 and 84) or (b) is at least 95% identical to SEQ ID NO:2 (*see* claims 100 and 109). *Such sequences are explicitly described in the specification.* As the Examiner recognizes, Applicant has clearly described SEQ ID NO:1 as a NES1 polypeptide and SEQ ID NO:2 as a nucleic acid sequence encoding a NES1 polypeptide (*see, e.g.*, Figures 10 and 11). Applicant has further clearly stated that one can carry out the methods now claimed by "measuring NES1 gene expression" (Office action at page 3, line 4) or by "determining whether the nucleic acid includes a mutated NES1 gene" (Office action at page 3, lines 32-33). Moreover, Applicant teaches that NES1 polypeptides useful in the invention can be at least 95% identical to SEQ ID NO:1 (specification at pages 6-7) or at least 95% identical to SEQ ID NO:2 (specification at page 9, lines 6-9). Those of ordinary skill in the art routinely compare nucleic acid and amino acid sequences in order to determine where, and to what extent, the sequences differ. Given Applicant's teaching that one sequence is at least 95% identical to another, one of ordinary skill in the art would readily recognize all of the species within the genus of the claim.

By way of illustration, a person of ordinary skill in the art, upon reading Applicant's specification, would find a description of methods of diagnosing a mammal by examining the expression of NES1 or by assessing NES1 for mutations (specification at page 3). They would also find the sequence of a NES1 cDNA (SEQ ID NO:2) and the encoded polypeptide (SEQ ID NO:1). In addition, they would find the statement that "[p]referably, such a polypeptide [*i.e.*, a NES1

polypeptide] has an amino acid sequence which is at least ... 95% identical to the amino acid sequence of the NES1 protein of Fig. 10 (SEQ ID NO:1)" (specification at pages 6-7; nucleic acid sequences that are at least 95% identical to SEQ ID NO:2 are described at page 9). Could that person then reasonably conclude that Applicant possessed methods using SEQ ID NO:1? Yes, certainly. Could that person also reasonably conclude that Applicant possessed methods requiring amino acids 1-270 of SEQ ID NO:1? Yes, as that sequence contains 98% of the 276 amino acids present in SEQ ID NO:1. Obviously, many other variants of SEQ ID NO:1 could be used in this illustration, and it would be just as readily apparent to one of ordinary skill in the art that Applicant possessed those sequences.

By setting out the sequence of SEQ ID NO:1 and by specifying that useful polypeptides include those having a particular degree of identity to SEQ ID NO:1, Applicant has described *all* of the species within the genus recited in the claims. *Writing out one exemplary sequence after another would add nothing more.* One of ordinary skill in the art would recognize Applicant's language as a conventional way of describing all of the species within a genus (*i.e.*, all of the sequences having a certain level of identity). Further, given Applicant's description, one of ordinary skill in the art would have no difficulty in concluding that Applicant was in possession of methods using the sequences described. For written description, nothing more is required.

The Examiner stated, "[t]o overcome the above rejection [for lack of an adequate written description], the claim must contain a structural feature *of the NES1 gene accompanied by a functional feature*" (Office action at page 4; emphasis added). New claims 82-93 and 94 were included in the rejection "because *the NES1 gene is not defined by structural and functional features*" (Office action at page 4; emphasis added).

The claims now include a structural limitation on the NES1 gene; the structure is limited with respect to SEQ ID NO:1 or SEQ ID NO:2. The claims now also include a functional limitation on the NES1 gene in the independent claims. Claims 69 and 100 require a biological sample comprising a NES1 gene, "the expression of which is down-regulated during tumorigenic progression." Similarly, claims 84 and 109 require a biological sample comprising a NES1 gene, "the mutation of which is

associated with tumorigenic progression." Thus, the NES1 gene must be one that functions – whether through altered expression or altered sequence – as an indicator of tumorigenic progression.

While the inclusion of this language satisfies the Examiner's request for a "functional feature" (Office action at page 4), for the record, Applicant contends that the written description requirement is met without the inclusion of functional limitations. The Written Description Guidelines instruct Examiners how to assess various written descriptions, including those that contain only an *incomplete* structure. The Guidelines read (page 1106, middle-column; emphasis added):

> *[if]* the application as filed does not disclose the complete structure ... of the claimed invention as a whole, [*then* an Examiner should] determine whether the specification discloses *other relevant identifying characteristics* sufficient to describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention.

The footnote to that passage, footnote 49, states (emphasis added):

> Thus, the written description requirement may be satisfied through disclosure of function and *minimal* structure when there is a well-established correlation between structure and function.

Here, Applicant has more than "minimal structure." Indeed, Applicant has provided the complete sequences of SEQ ID NO:1 and SEQ ID NO:2 and has described the particular and readily identifiable variants that can be used in the methods now claimed. Applicant has also demonstrated a correlation between NES1 expression and tumor progression (the Examiner's attention is directed to the results presented in Table 1). As one of ordinary skill in the art would find, upon reading Applicant's description, particular NES1 sequences; a description of all of the species within a given NES1 genus (*i.e.*, a description of sequences exhibiting a particular level of identity to a reference sequence); and evidence that NES1 expression indicates the presence of a malignancy, one of ordinary skill in the art would conclude that Applicant was in possession of the methods now claimed. Applicant's written description is adequate.

Enablement: The Examiner states that claims 69-75, 82-93 and 95 are rejected "for lack of enablement for the reasons set forth in the prior Office action dated December 19, 2003" (Office

action at page 4). Similarly, the Examiner states that "[t]he previous Office action sets out a *prima facie* case of non-enablement" (Office action at page 4).

With respect to the prior action, Applicant notes that, *at that time*, the pending claims encompassed methods that were considerably broader than those now claimed. The scope of the claims should be considered in an analysis of enablement (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), and the present claims are now limited to methods that require a biological sample from a human patient (the claims originally examined recited "mammals" rather than "a human"). Moreover, the NES1 gene examined within the sample must either include a coding sequence that encodes a polypeptide that is at least 95% identical to SEQ ID NO:1 (*see* claims 69 and 84) or that is at least 95% identical to SEQ ID NO:2 (*see* claims 100 and 109). Further regarding claim scope, and in view of Applicant's description of a NES1 polypeptide, the Examiner interpreted the NES1 gene in the prior claims as (Office action at page 4; emphasis added):

> Any human gene which encodes a polypeptide having *at least 45% identity* to the amino acid sequence of SEQ ID NO:1, and is a cell cycle-regulated serine protease whose expression negatively correlates with the presence of malignant epithelial cells.

As noted, the required degree of identity now recited in each of the independent claims is much higher than 45% (and, it is the claims – not the disclosure generally – that must be enabled). The Examiner also states (Office action at page 4):

> Enablement requires a disclosure sufficient to allow a person of skill in the art to practice the full scope of the claimed invention without undue experimentation.

However, the standard is not as high as the Examiner states (*i.e.*, to the "full scope" of the claimed invention). To the contrary, the scope of enablement must only bear a *reasonable correlation* to the scope of the claims. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The Examiner also argues that "Applicants make no effort to explain why they consider the disclosure of a cDNA of SEQ ID NO:2 would enable the scope of the claimed methods as defined above" (Office action at page 4). To the contrary, Applicant has pointed out, and wishes to reiterate, that (1) the present specification provides a complete target sequence (indeed, it

discloses the polypeptide sequence of SEQ ID NO:1 and the nucleic acid sequence of SEQ ID NO:2 as recited in the present claims); (2) methods of assessing gene expression are routinely carried out by those of ordinary skill in the art; and (3) the scope of the claims had been limited to assessing a human NES1 gene in a human sample. Indeed, the present claims have been further restricted to analysis of a NES1 gene having the functional and structural limitations now required by reference to 95% identity. These facts are clearly each related to one of the "Wands factors" and when those factors are properly weighed, one should find enablement. Given Applicant's specification, including the description of NES1, the numerous methods described for assaying gene expression (including methods that have been practiced for many, many years, and which are carried out routinely by graduate students), and Applicant's success in correlating NES1 expression with tumorigenicity, one of ordinary skill in the art could readily practice the methods now claimed. The level of skill in the art is high. In view of these factors, the scope of enablement provided by the specification bears more than a reasonable correlation to the scope of the claims. This ground for rejection should be withdrawn.

35 U.S.C. § 112, Paragraph 2

The Examiner rejected claims 84-95 "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office action at page 5). The Examiner states that claim 84, including a step of examining the sequence of the NES1 gene, where a mutation in the gene indicates that the human has a carcinoma or an increased likelihood of developing a carcinoma, and claim 94, which stipulates that the mutation is relative to the sequence of SEQ ID NO:2, are indefinite. The Examiner asserts that silent mutations, mutations in noncoding regions of SEQ ID NO:2, or mutations resulting in conserved amino acid changes would not be expected to have a significant diagnostic value.

Claim 84, from which claims 85-93 and 95 depend (claim 94 has been canceled), has been amended. Claim 84 requires step (a), which reads (emphasis added):

> (a) providing a biological sample from a human, *wherein the biological sample comprises a NES1 gene, the mutation of which is associated with tumorigenic progression* and the sequence of which comprises a coding sequence that encodes a polypeptide that is at least 95% identical to SEQ ID NO:1; and

Thus, the gene included in the sample and further assessed in step (b) is a NES1 gene that, when mutated, is an indicator of tumorigenic progression. Thus, one of ordinary skill in the art would see the metes and bounds of the claim as excluding mutations that do not have diagnostic value. Accordingly, Applicant requests the Examiner to reconsider and withdraw this ground for rejection.

The Examiner rejected claim 91 as being indefinite because the phrase "or altered binding or cleavage activity" "does not clearly set forth the metes and bounds of the patent protection desired...[I]t is not clear from the claim or the specification to what the amplified [NES1] nucleic acid sequence binds or what activity it does have" (Office action at page 5).

Claim 91 has been amended to delete the phrase considered indefinite. Therefore, this ground for rejection is moot and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicant contends the present claims are now in condition for allowance, which action is respectfully requested. *Should the Examiner maintain any of the present grounds for rejection, the favor of a telephone call to the undersigned is respectfully requested.*

Filed herewith is a Petition for Extension of time, to and including January 24, 2005 (January 22, 2005, being a Saturday). Also enclosed is a check for the required fee. Please apply any other charges or credits to deposit account 06-1050 referencing Attorney Docket No. 00398-100005.

Respectfully submitted,

Date: January 24, 2005

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